REMARKS

Claims 6-13 are under consideration in the current application. Claims 1-5 and 14-20 were previously withdrawn as being drawn to the non-elected invention.

By way of the present amendment, claims 7 and 9 are amended herein.

Formal Matters

Applicants thank the Examiner for entering and examining the claims filed October 1, 2007 with the correct mark-ups shown in the claim submission of August 23, 2007. Applicants submit, herein, a new marked-up copy of the presently amended claims on which this response is based.

Applicants note that on form PTOL-326 of the present Office Action, there is no reference to claim 6. However, page 2 of the Office Action indicates that claim 6 is pending. Appropriate correction of form PTOL-326 is therefore requested.

Amendments to Claims

Claim 7 has been amended to recite "said method comprising administering to said mammal an IL-1α release inhibiting amount of a copper chelator, thereby inhibiting said macrophage infiltration, wherein said IL-1α release is non-traditional IL-1α release." Support for these amendments is found on page 9, paragraph 50; page 12, paragraphs 71, 72, and 74; page 14, paragraph 79, line 8; page 16, paragraph 90, line 4; page 16, paragraph 92, line 2; and page 25, paragraphs 138-140 in the specification.

Claims 9 has been amended to recite "said method comprising administering an IL-1α release inhibiting amount of a copper chelator to a mammal, thereby inhibiting said cell proliferation, wherein said IL-1α release is non-traditional IL-1α release." Support for these amendments is found on page 9, paragraph 50; page 12, paragraphs 71, 0072, and 74; page 14, paragraph 79, line 8; page 16, paragraph 90, line 4; page 16, paragraph 92, line 2; and page 25, paragraphs 141 and 142 in the specification.

No new matter is added by way of these amendments.

Rejection of claim 6 pursuant to 35 U.S.C. § 102(b)

The Examiner has rejected claim 6 as being anticipated by Applebaum et al., 1990, Free Rad. Biol. Med. 8:133-43 (hereafter referred to as "Applebaum"). The Examiner alleges that Applebaum teaches the effect of neocuproine, a copper and iron chelator, on cardiac injury. It is the Examiner's view that the pending claims recite using a known composition (a copper chelator) and that the claimed use is a result or property of that structure. Without stating so explicitly, it appears that the Examiner is alleging that Applebaum inherently teaches the claimed invention.

With respect to the law of inherent anticipation, it is well established that the mere recitation of a newly discovered function or property, inherently possessed by *things* in the prior art, does not cause a claim drawn to those *things* to distinguish over the prior art (See *In re Swinehart*, 439 F.2d at 212-213). Thus, inherency law is more applicable to composition claims. Here, claim 6 is directed to a method of inhibiting IL1-α release from a cell, or the use of a copper chelator to inhibit IL1-α release from a cell for inhibiting neointima formation following vessel injury. Neointima formation is a natural response of the arterial wall to injury and is based on time-dependent infiltration of the arterial wall with inflammatory cells, growth factors and cytokines. This leads to the migration of smooth muscle cells from the vessel media to the intima where they proliferate and deposit extracellular matrix. This negative remodeling of the vessel wall is comparable to the formation of a scar in response to injury.

Applebaum discloses a method of preventing cardiac electrical disordered electrical activity (arrhythmia) such as ventricular fibrillation and ventricular tachycardia of cardiac muscle that occur as a result of cardiac reperfusion. The primary causes of arrhythmic generation are chemically defined substances produced and accumulated in myocardium during reperfusion. These chemical mediators of reperfusion arrhythmias modulate of cardiac cellular electrophysiology by complex changes at the level of cardiac ion channels. Specifically, Applebaum teaches that arrhythmias associated with cardiac reperfusion may be attributable to the ability of transition metals such as iron and copper to catalyze the formation of the very reactive and deleterious hydroxyl radical. Methods of preventing electrical arrhythmias as a result of cardiac reperfusion, specifically ventricular fibrillation and ventricular tachycardia, as disclosed in Applebaum, cannot anticipate, either inherently or otherwise, a method of inhibiting neointima formation

where the method comprises inhibiting IL1-α release from a cell. Ventricular fibrillation and ventricular tachycardia that result from cardiac reperfusion are distinct pathophysiological events from neointima formation. These disparate conditions occur over a different time scale, have a different etiology, and require vastly different treatment protocols. Because of the differences in etiology, duration, and treatment, a method of treating arrhythmia cannot be considered to inherently treat neointima formation.

It is well-established law that "[a] claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference." MPEP §2131 (quoting *Verdegaal Bros. v. Union Oil Co. of Calif.*, 2 USPQ2d 1051, 1053 (Fed. Cir. 1987)). "The identical invention must be shown in as complete detail as is contained in the . . . claim." *Id.* (quoting *Richardson v. Suzuki Motor Co.*, 9 USPQ2d 1913, 1920 (Fed. Cir. 1989) (emphasis added). Therefore, in order to anticipate these claims under 35 U.S.C. §102(b), Applebaum must describe each and every element of claim 6. Applebaum does not meet this standard. Claim 6 is directed to a method of inhibiting neointima formation by administering a copper chelator to a mammal such that non-traditional IL-1α release is inhibited, thereby inhibiting subsequent neointima formation.

Applebaum uses chelating agents to remove and/or alter the redox potential of redox-active metals. Nowhere does Applebaum disclose the element of IL1-α release, a method of inhibiting IL1-α release from a cell, or the use of a copper chelator to inhibit IL1-α release from a cell. Importantly, the instant specification makes it clear that the claimed effect on IL1-α release from a cell is not inherent in the mere chelation of copper. Specifically, on page 33, paragraph 180, and page 35, paragraph 188, the specification discloses that IL1-α release is also inhibited by expression of a truncated form of the Ca^{2+} binding protein, S100A13. Thus, the key element in the present invention is preventing the formation of a multimolecular aggregate required for IL1-α release from a cell. In addition, Applebaum does not teach a method for inhibiting neointima formation following vessel injury. Thus, Applebaum does not anticipate each and every element of the present claimed invention and the rejection should be withdrawn.

Rejection of claims 6, 9, and 11-13 pursuant to 35 U.S.C. § 102(b)

Claims 6, 9, and 11-13 stand rejected under 35 U.S.C. § 102(b) as being anticipated by Brewer et al., (WO 200013712; hereafter referred to as "Brewer"). In order to anticipate these claims under 35 U.S.C. §102(b), Brewer must describe each and every element of claims 6, 9, and 11-13. Brewer does not meet this standard.

Brewer teaches a method of treating neovascularization, aberrant vascularization, and aberrant angiogenesis by administering the copper chelator tetrathiomolybdate to induce mild systemic copper deficiency as a method of treating solid tumors in patients with cancer, as well as other diseases with an angiogenic component.

Brewer cannot anticipate the presently claimed invention because Brewer (1) does not disclose the claimed element of inhibiting IL1-α release from a cell, or the use of a copper chelator to inhibit IL1-α release from a cell. Nor does Brewer teach a method to prevent (2) neointima formation following vessel injury (claim 6); (3) cell proliferation associated with arterial wall injury (claim 9); (4) secretion of extracellular matrix following arterial injury (claim 11); or (5) neointimal thickening associated with arterial wall injury (claim 12). Of the pending claims, only claim 13 is directed to a method of inhibiting adventitial angiogenesis, however the method comprises the essential step of inhibiting IL1-α release. Thus, Brewer does not describe each and every element of claims 6, 9, and 11-13.

In addition, a method of treating neovascularization, aberrant vascularization, aberrant angiogenesis to treat solid tumors, wet type macular degeneration or rheumatoid arthritis as taught by Brewer, cannot anticipate a method of inhibiting IL1-α release from a cell, or the use of a copper chelator to inhibit IL1-α release from a cell for inhibiting neointima formation following vessel injury (claim 6); cell proliferation associated with arterial wall injury (claim 9); secretion of extracellular matrix following arterial injury (claim 11); or neointimal thickening associated with arterial wall injury (claim 12), either inherently or otherwise.

Pathological neovascularization and aberrant angiogenesis are defined by the growth of new blood vessels, a hallmark of tumorigenesis. Neointima formation, cell

proliferation, and secretion of extracellular matrix associated with arterial wall injury are all part of a blood vessel's response to injury and are involved in scar formation at the site of injury. Neointima formation, cell proliferation, and secretion of extracellular matrix do not involve either aberrant angiogenesis or neovascularization as part of their pathology, nor are they themselves components of aberrant angiogenesis or neovascularization. Nor are the etiologies of aberrant angiogenesis and neovascularization inherent in or even necessarily related to the etiologies of neointimal formation, cell proliferation, or secretion of extracellular matrix associated with arterial wall injury. Thus a method of treating neovascularization, aberrant vascularization, and aberrant angiogenesis cannot anticipate a method of inhibiting IL1-α release from a cell, or the use of a copper chelator to inhibit IL1-α release from a cell to prevent neointima formation following vessel injury (claim 6); cell proliferation associated with arterial wall injury (claim 9); secretion of extracellular matrix following arterial injury (claim 11); neointimal thickening associated with arterial wall injury (claim 12), or adventitial angiogenesis associated with arterial wall injury (claim 13).

Also, as noted above, the instant specification makes it clear that the claimed effect on IL1-α release from a cell is not inherent in the mere chelation of copper (page 33, paragraph 180, and page 35, paragraph 188) since IL1-α release is also inhibited by expression of a truncated form of the Ca^{2+} binding protein, S100A13. Thus, the key element in the present invention is preventing the formation of a multimolecular aggregate required for IL1-α release, and consequently inhibiting IL1-α release from a cell.

Claims 6 and 11-13 all encompass a method of inhibiting IL1-α release. In an effort to expedite prosecution, applicants have amended claim 9, herein, to recite "...an IL1- α release inhibiting amount of a copper chelator...".

For the above reasons, Brewer does not anticipate the present claimed invention and the rejection of these claims should be reconsidered and withdrawn.

Rejection of claims 7-13 pursuant to 35 U.S.C. § 103(a)

The Examiner has rejected claims 7-13 under 35 U.S.C. §103(a) as being obvious over Brewer et al., (WO 200013712), Wang et al., 2000, Biochem. Biophys. Res.

Commun. 271:138-143 (hereafter referred to as "Wang"); and Wempe et al., 1997, Arterioscler. Thromb. Vasc. Biol. 17:2471-8 (hereafter referred to as "Wempe").

The test which must be met for a reference or a combination of references to establish obviousness has not been satisfied in the instant matter. The MPEP states, in relevant part, the proper test for obviousness:

> Office policy is to follow *Graham v. John Deere Co.* in the consideration and determination of obviousness under 35 U.S.C. 103... [T]he four factual inquires enunciated therein as a background for determining obviousness are as follows:
> (A) Determining the scope and contents of the prior art;
> (B) Ascertaining the differences between the prior art and the claims in issue;
> (C) Resolving the level of ordinary skill in the pertinent art; and
> (D) Evaluating evidence of secondary considerations. MPEP § 2141.

Additionally, MPEP § 2143.01 provides: "The mere fact that references can be combined or modified does not render the resultant combination obvious unless the prior art also suggests the desirability of the combination. *In re Mills*, 916 F.2d 680, 16 USPQ2d 1430 (Fed. Cir. 1990)." (emphasis added).

Further, it is well-established law that each prior art reference must be evaluated in its entirety, and all the prior art must be evaluated as a whole. *Hughes Aircraft Co. v. United States*, 15 Cl. Ct. 267, 272 (Ct. Cl. 1988), citing *Panduit Corp. v. Dennison Manufacturing Co.*, 774 F.2d 1082, 1093-94 (Fed. Cir. 1985), *vacated*, 475 U.S. 809 (1986), *on remand*, 810 F.2d 1561 (Fed. Cir. 1987), *cert. denied*, 481 U.S. 1052 (1987).

The deficiencies of Brewer have been discussed in detail above and are not repeated here. Briefly, Brewer cannot render the instant invention obvious because a method of using a copper chelator to treat neovascularization and aberrant angiogenesis of tumors, wet type macular degeneration, or rheumatoid arthritis, as taught by Brewer, provides no teaching that would lead a skilled artisan to arrive at a method of inhibiting IL1-α release from a cell to prevent macrophage infiltration following vessel injury (claims 7 and 8); cell proliferation associated with arterial wall injury (claims 9 and 10); secretion of extracellular matrix following arterial injury (claim 11); neointimal

thickening associated with arterial wall injury (claim 12), or adventitial angiogenesis associated with arterial wall injury (claim 13).

The Examiner has rejected claims 7-13 under 35 U.S.C. §103(a) as being obvious over Wang. Wang discloses an up-regulation of the expression of IL-1β, IL-1 receptor antagonist (IL-1ra), and IL-1 receptor (IL-1RI and IL-1RII) mRNA in carotid artery after balloon angioplasty, leading Wang to conclude that IL-1β, IL-1ra, IL-1RI, and IL-1RII may play a role in neointima formation. Further, on page 140, column 1, first full paragraph of the Results section, Wang specifically states that "No signal was detected for IL1-α mRNA expression in the carotid artery after balloon angioplasty, (emphasis added)," indicating that IL1-α expression is not required for neointima formation. Thus, Wang teaches away from the present invention. Accordingly, when viewed in its entirety, Wang alone cannot render the present invention obvious because Wang suggests that IL1-α is not an essential component of neointima formation. This is in direct contrast to the present invention which establishes that inhibiting IL1-α release from a cell is essential to inhibiting macrophage infiltration following vessel injury (claims 7 and 8); cell proliferation associated with arterial wall injury (claims 9 and 10); secretion of extracellular matrix following arterial injury (claim 11); neointimal thickening associated with arterial wall injury (claim 12), or adventitial angiogenesis associated with arterial wall injury (claim 13).

Together, Wang and Brewer do not arrive at the present invention, since neither teaches the essential element of inhibiting IL1-α release from a cell, or the role of IL1-α release in macrophage infiltration following vessel injury (claims 7 and 8); cell proliferation associated with arterial wall injury (claims 9 and 10); secretion of extracellular matrix following arterial injury (claim 11); neointimal thickening associated with arterial wall injury (claim 12), or adventitial angiogenesis associated with arterial wall injury (claim 13). Thus, neither Wang nor Brewer can be used to redress the deficiencies of the other to render the present invention obvious.

The Examiner has rejected claims 7-13 under 35 U.S.C. §103(a) as being obvious over Wempe. Wempe discloses preferential adhesion of monocytic cells to migrating endothelial cells after balloon denudation injury. Wempe also teaches that mRNA expression for the chemokine MCP-1 is increased in aorta endothelial cells after

balloon denudation injury. Wempe further discloses that endothelial cells stimulated with basic fibroblast growth factor (bFGF) have greater expression of MCP-1 than unstimulated cells, leading Wempe to suggest that bFGF may act as an autocrine regulator of endothelial cell activity and inflammatory cell trafficking.

Wempe does not teach a role for IL1-α in monocyte adhesion. Further, Wempe does not teach a method of inhibiting IL1-α release from a cell, the use of a copper chelator to inhibit IL1-α release from a cell, or a method to prevent macrophage infiltration (claims 7 and 8) by inhibiting IL1-α release from a cell. Wempe would not direct a skilled artisan to the present invention because Wempe teaches the importance of bFGF in MCP-1 expression and consequently suggests that bFGF is a mediator of inflammatory cell trafficking following balloon denudation injury. Because the mechanism of regulating MCP-1 expression by bFGF stimulation of endothelial cells as taught by Wempe neither predicts nor suggests the effect of IL1-α on macrophage infiltration or a method of inhibiting IL1-α release from a cell, Wempe would not lead a skilled artisan to arrive at the present invention comprising a method of inhibiting IL1-α release from a cell or the use of a copper chelator to inhibit IL1-α release from a cell to prevent macrophage infiltration. Nor does the mechanism elucidated by Wempe suggest a method to prevent cell proliferation associated with arterial injury (claims 9 and 10), secretion of extracellular matrix following arterial injury (claim 11) or neointimal thickening (claim 12) that encompasses inhibiting IL1-α release from a cell. Accordingly, the present invention cannot be obvious over Wempe, alone.

Further, since none of the references cited by the Examiner disclose the essential element of the invention, namely a method of inhibiting IL1-α release from a cell to prevent macrophage infiltration following vessel injury (claims 7 and 8); cell proliferation associated with arterial wall injury (claims 9 and 10); secretion of extracellular matrix following arterial injury (claim 11); neointimal thickening associated with arterial wall injury (claim 12), or adventitial angiogenesis associated with arterial wall injury (claim 13), none of the cited references can cure the deficiencies of the others. In an effort to expedite prosecution Applicants amend claim 7, herein, to recite "...an IL1- α release inhibiting amount of a copper chelator...". However, for the reasons set forth above, Applicants respectfully submit that the rejection of claims 7-13 under 35

U.S.C. § 103(a) is improper and does not apply. Applicants respectfully request reconsideration and withdrawal of the rejection.

Summary

Applicants respectfully submit that the pending claims, including the amended claims, are fully supported in the specification as filed, and that no new matter has been added by way of the present Amendment and Response.

Favorable examination and allowance of the claims is hereby requested.

Respectfully submitted,
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